Multimodality Tachycardia-Induced Stress Testing Predicts a Low-Risk Group for Early Cardiovascular Mortality After Renal Transplantation

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Nicholas J. Montarello[1,4], Tania Salehi[2,4], Alex P. Bate[1], Anthony D. Pisaniello[3], Philip A. Clayton[2,3], Karen S.L. Teo[1], Matthew I. Worthley[1,3] and Patrick T. Coates[2,3]

[1]Department of Cardiology, Central Adelaide Local Health Network, Adelaide, Australia; [2]Central Northern Adelaide Renal and Transplantation Service, Adelaide, Australia; and [3]The University of Adelaide, Adelaide, Australia

Background: Cardiovascular events remain a major cause of death in kidney transplant recipients. The optimal noninvasive workup to prevent peritransplant cardiac mortality remains contentious.

Methods: We conducted a retrospective analysis to assess the renal transplantation cardiovascular assessment protocol within a single-center population over a 5-year period. Asymptomatic patients aged less than 45 years with no history of cigarette smoking, without diabetes mellitus, and dialysis-dependent for less than 24 months did not undergo cardiac testing before listing. All other asymptomatic patients underwent a noninvasive, tachycardia-induced stress test, where a target heart rate of 85% predicted for age and gender was required. The primary endpoints were rates of acute myocardial infarction (AMI) and cardiovascular death at 30 days after renal transplantation.

Results: Between 2015 and 2019, 380 recipients underwent cardiac evaluation: 79 (20.8%) were deemed low cardiovascular risk and placed on the renal transplant waitlist without further assessment; 270 (71.1%) underwent a tachycardia-induced stress test; and 31 (8.1%) were deemed high risk and proceeded directly to invasive coronary angiography (ICA). In the 5-year follow-up, 3 patients (0.8%) experienced an AMI 30 days after renal transplantation, all of which occurred in the high-risk "direct to ICA" cohort. No events were documented in the low-risk cohort or in patients who had a negative tachycardia-induced stress test. There were no cardiovascular deaths within 30 days after transplantation.

Conclusion: A negative tachycardia-induced cardiac stress test, achieving 85% of predicted heart rate, was associated with a 0% AMI rate and no cardiovascular deaths at 30 days after renal transplantation.

K idney transplantation provides significant long-term survival benefit compared with chronic renal replacement therapy (RRT).[1] Although cardiovascular events remain a major cause of morbidity and mortality in kidney transplant recipients, identifying myocardial ischemia in asymptomatic individuals and initiating treatment remains a contentious issue.[2,3]

Chronic kidney disease (CKD) is an independent risk factor for the development of both coronary artery disease (CAD) and more extensive and severe coronary heart disease.[4–6] In addition, patients with end-stage kidney disease (ESKD) frequently have additional, multiple, traditional and nontraditional atherosclerotic risk factors that further increase the incidence of CAD.[7–10] CKD is also associated with a poorer prognosis after presentation with acute coronary syndrome, percutaneous coronary intervention (irrespective of whether stenting is performed), and coronary artery bypass surgery (CABG).[6,11–13]

Invasive coronary angiography (ICA) remains the reference gold standard investigation for the diagnosis of significant epicardial CAD, but its limitations include the associated risks to the patient, including radiation

Correspondence: Patrick T. Coates, Central Northern Adelaide Renal and Transplantation Service, Royal Adelaide Hospital, Port Road, Adelaide, SA, 5000, Australia. E-mail: Toby.Coates@sa.gov.au

[4]NJM and TS are co-first authors.

exposure and contrast dependence, worsening kidney function (1 in 200 cases performed), contrast reactions (1 in 250 cases performed), vascular complications (1 in 200 cases performed), periprocedural acute myocardial infarction (AMI; 1 in 2000 cases performed), periprocedural stroke (1 in 1500 cases performed), and periprocedural death (1 in 1000 cases performed). Furthermore, ICA is a form of anatomic assessment and, when used in isolation, is unable to evaluate the presence of myocardial ischaemia. It is therefore an inappropriate "universal" initial diagnostic investigation for risk stratification during renal transplant workup. A variety of noninvasive tests can be used to evaluate possible obstructive CAD. These tests are categorized as anatomic or functional. Computed tomography coronary angiography (CTCA) is a form of anatomic assessment. The available functional coronary artery tests include exercise stress electrocardiography (ECG), stress echocardiography (exercise or dobutamine induced), stress myocardial perfusion scintigraphy (exercise, adenosine, dipyridamole, or dobutamine induced), and stress cardiac magnetic resonance (cMRI) imaging (adenosine or dobutamine induced). These tests are further divided according to the method used to induce ischemia and include tachycardia-based tests via exercise, pacing, or dobutamine and pharmacologic provocation via vasodilation using adenosine or dipyridamole.

Cardiovascular risk assessment is mandatory in our center before listing for renal transplantation. At present, asymptomatic patients are excluded from investigation if they are nonsmokers, under age 45 years, have no history of diabetes mellitus, or have commenced dialysis within the previous 24 months. These patients can be listed for renal transplantation without more formal assessment of their coronary artery status. For all other asymptomatic patients, a noninvasive, tachycardia-induced stress test is recommended as the preliminary investigation to rule out physiologically significant CAD. For a tachycardia-induced stress test to be considered diagnostic, a target heart rate of 85% predicted for age and gender must be achieved. If this target heart rate is not reached on an initial or subsequent attempt or the tachycardia stress test is positive for myocardial ischemia, ICA is required before a patient can be placed on the active renal transplant list. Furthermore, symptomatic patients were initially referred through for an invasive coronary angiogram.

The primary endpoint of this retrospective analysis was aimed at evaluating the effectiveness of a negative tachycardia-induced cardiac stress test to accurately predict the risk of perioperative renal transplant myocardial infarction and cardiovascular death.

METHODS

Study Design
We conducted a retrospective review on our single center population of renal transplant recipients between January 2015 and December 2019. Participants were identified through the center's renal transplant database. Once identified, patient information was collected through the Royal Adelaide Hospital medical records. Additional data was obtained from the Australia and New Zealand Dialysis & Transplant (ANZDATA) registry. Patients were followed up to a maximum of 12 months after renal transplantation.

The retrospective review was granted approval by the center's ethics committee.

Population
The participants included adult (age >18 years) live and deceased donor kidney-only transplant recipients, with transplantation conducted at our center between 1 January 2015 and 31 December 2019. The deceased donor kidney cohort included donation after both circulatory death (DCD) and brainstem death (DBD).

The patients studied were those who had fulfilled the center's cardiovascular assessment protocol and had proceeded to renal transplant surgery. This included patients considered at low risk for a periprocedural cardiovascular event on clinical grounds who had therefore not undergone cardiac stress testing, as well as patients undergoing tachycardia-induced noninvasive coronary stress testing. Patients with no evidence of reversible ischemia on a valid coronary stress test who went on to renal transplantation without further invasive coronary imaging (ICA) were the principle cohort that was studied for our primary hypothesis. Patients undergoing ICA following a positive tachycardia-induced coronary stress test or following an indeterminate coronary stress test (unable to reach 85% of the predicted maximal heart rate response) were also followed up with regards to our prespecified endpoints and provided a comparator. The outcome of ICA including complications and subsequent revascularization were recorded. Patients were excluded from the analysis if they had a vasodilation based pharmacologic coronary stress test or a nonfunctional anatomic coronary assessment.

Imaging Protocols
Exercise stress ECG was performed on a treadmill using the Modified Bruce Protocol to predict target heart rate. Exercise and dobutamine-induced stress echocardiography used standard parasternal long- and short-axis images and apical 4- and 2-chamber views for assessment of regional wall motion abnormalities. Exercise- and dobutamine-induced stress myocardial perfusion

scintigraphy involved administration of 99mTc-Sestamibi to identify myocardial perfusion defects. Dobutamine-induced stress cMRI imaging was performed on a 1.5T Siemens Aera scanner. Gadolinium contrast was not used.

Dobutamine used for stress echocardiography, myocardial perfusion scintigraphy, and cMRI was infused at a rate of 5 mcg/kg/min for 3 min, incremented to 10, 20, 30, and 40 mcg/kg/min at 3-min intervals until the target heart rate was achieved. If the target heart was not achieved at the maximal infusion rate, intravenous atropine was administered to a maximum dose of 1200 mg.

Imaging was performed at baseline, peak heart rate, and in the recovery phase for both exercise and dobutamine-induced stress echocardiography. Stress echocardiography and cMRI were considered to be positive for ischemia if 1 or more segments of left ventricular myocardium worsened in function during stress from normokinesis to hypokinesis, akinesis, or dyskinesis. With regard to scintigraphy, fixed defects were distinguished from reversible ones, both qualitatively and quantitatively, using polar maps with a 20 segment score model to generate a sum difference score. A rest study was often omitted in normal scans to limit radiation exposure. Scans were reported by an unblinded senior nuclear medicine physician.

Beta-blockers were withheld for 72 h before tachycardia-induced stress testing. Consultation with a cardiologist was mandated if blood pressure exceeded 180/90 mm Hg before scheduled stress testing.

Patient Characteristics

Demographics including patient age, gender, and ethnicity, together with patient data including body mass index, primary renal disease, duration of ESKD, nature of transplantation, previous history of coronary artery disease, previous history of stroke, previous history of peripheral vascular disease, and atherosclerotic risk factors including diabetes mellitus and smoking status, were documented.

Endpoints

The primary endpoint was the effectiveness of a negative tachycardia-induced stress test in assessing the composite of AMI and cardiovascular death within 30 days after renal transplantation. AMI was defined by the Fourth Universal Definition of myocardial infarction with a typical rise and/or fall in troponin with at least 1 value >99th percentile upper range limit.[14] Cardiovascular death was defined as sudden cardiac death or death resulting from an AMI, heart failure, cardiovascular procedures, stroke, or cardiovascular hemorrhage.

The secondary endpoints included the presence of obstructive coronary artery disease on ICA performed after a positive or indeterminate tachycardia-induced coronary stress test. Obstructive coronary artery disease was defined as the presence of a 70% or greater reduction in diameter of 1 or more major epicardial coronary vessels as assessed by 2 independent, experienced, interventional cardiologists. Additional secondary endpoints included ICA related death, AMI, stroke, or major access site bleeding, and cardiovascular death in the presence of a functioning allograft within the first year of transplantation.

Statistical Analysis

Primary and secondary endpoints were reported as proportions of the sample size. Positive predictive values were reported for the relevant tachycardia-induced stress tests.

Analyses were conducted with the use of OpenEpi version 3.0; https://www.openepi.com/Menu/OE_Menu.htm.

RESULTS

Study Population

During the study period between January 2015 and December 2019, 399 patients received kidney-only transplants within Central Northern Adelaide Renal Transplant Service (Figure 1). Six patients had CTCA and 13 patients had a vasodilatory myocardial perfusion test; these patients were excluded from the study. Seventy-nine (20.8%) patients were deemed low risk as per protocol and were listed for renal transplantation with no additional cardiovascular assessment: 1 patient did not meet prespecified criteria for exclusion from provocative testing, which was a protocol breach. A total of 270 patients (71.1%) proceeded with noninvasive, tachycardia-induced coronary assessment: 11 had an exercise stress ECG (4.1%), 42 had exercise stress echocardiography (ESE) (15.6%), 16 had a dobutamine stress echocardiogram (DSE) (5.9%), 109 had an exercise myocardial perfusion scintigram (40.4%), 78 had a dobutamine stress myocardial perfusion scintigram (28.9%), and 14 had a dobutamine stress cMRI (5.2%). Thirty-one patients (8.1%) proceeded directly to ICA based on their risk profile with no preceding provocative coronary investigation: 2 in the context of workup for cardiac valve surgery, 5 due to dilated cardiomyopathy on baseline transthoracic echocardiography, and 24 because of concerning symptomatology for coronary ischemia.

During the study period, 8 patients were deemed unsuitable for kidney transplantation after completion of the cardiovascular assessment protocol and consequently were not waitlisted.
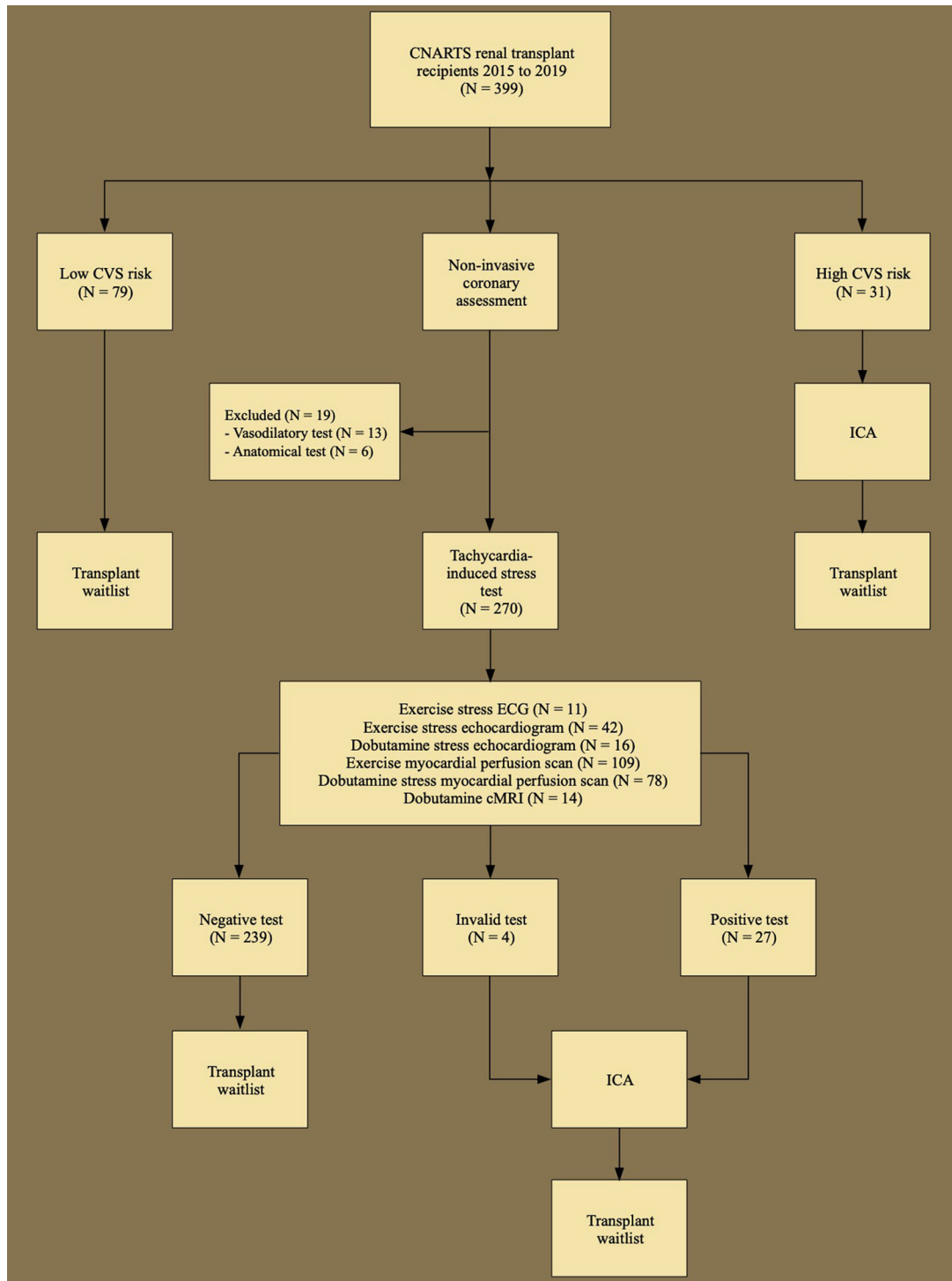
Figure 1. CONSORT diagram. cMRI, cardiac magnetic resonance imaging; CNARTS, Central Northern Adelaide Renal Transplant Service; CONSORT, Consolidated Standards of Reporting Trials; CVS, cardiovascular system; ECG, electrocardiography; ICA, invasive coronary angiography.

Baseline Characteristics

Table 1 shows the baseline demographic and clinical characteristics of the patients enrolled in the trial. The mean duration of follow-up was 354 days.

Noninvasive Investigation Results

Of the 270 tachycardia-induced cardiac stress tests performed, 27 tested positive at 85% or greater maximum predicted heart rate, and 239 tested negative for reversible myocardial ischaemia. All 27 patients with a positive result proceeded to ICA. In addition, there were 4 patients who proceeded to ICA after invalid tachycardia-induced provocative testing (i.e., failing to reach a target heart rate of 85% maximum predicted for age and gender).

Table 1. Demographic, clinical, and laboratory characteristics of patients at baseline[a]

Characteristics	CNARTS renal transplant recipients (N = 380)[b]
Age (yr)	52.0 ± 13.3
Male sex, n (%)	225 (59%)
Ethnicity	
Caucasian	274 (72%)
Indigenous	49 (13%)
Asian	42 (11%)
Other	15 (4%)
BMI (kg/m²)	27.5 ± 5.6
Diabetes mellitus	112 (29%)
Smoking status[c]	166 (44%)
Duration of ESKD (yr)	4.0 ± 6.0
Primary renal disease	
Diabetes mellitus	72 (19%)
Hypertension	16 (4%)
Glomerulonephritis	136 (36%)
PCKD	55 (15%)
Reflux nephropathy	27 (7%)
Other	31 (8%)
Unknown	43 (11%)
Coronary artery disease	44 (12%)
Previous stroke	15 (4%)
Peripheral vascular disease	18 (5%)
Donation pathway	
Live	77 (20%)
DBD	223 (59%)
DCD	80 (21%)
Preemptive renal transplant	32 (8%)
First renal allograft	330 (87%)

BMI, body mass index; DBD, donor after brain death; DCD, donor after cardiac death; ESKD, end stage kidney disease; PCKD, polycystic kidney disease.
[a]Plus–minus values are means ± SD. Percentages may not total 100 because of rounding.
[b]Renal transplant recipients who underwent vasodilatory or anatomic tests excluded (n = 19).
[c]Current or former smoking history.

Of the 27 positive tachycardia-induced cardiac stress tests, 1 was determined by an EST, 6 by DSE, 3 by an exercise myocardial perfusion scintigram, 15 by a dobutamine myocardial perfusion scintigram, and 2 by a dobutamine stress cMRI.

Of the 239 patients with a negative tachycardia-induced cardiac stress test result, the mean peak heart rate achieved was 88.1% ± 5.5% of the maximum predicted for age and gender. In a breach of protocol, 6 patients (2.5%) did not achieve the 85% predicted heart rate target but were still classified as having a negative provocative investigation and went on to the active transplant waitlist.

Primary Endpoints

Within 30 days of renal transplantation, no AMI or cardiovascular deaths were identified in patients who had a negative "tachycardia-induced" stress test. Furthermore, there were no cardiovascular deaths in the 30-day period after renal transplantation in the entire cohort and also there were no AMIs within 30

Table 2. Endpoints

	CNARTS renal transplant recipients (N = 380)[a]		
	Low CVS risk[b] (n = 79)	Tachycardia-induced stress test (n = 270)	High CVS risk[c] (n = 31)
Primary endpoints			
AMI within 30 d	0 (0.0%)	0 (0.0%)	3 (9.7%)
Cardiovascular death within 30 d	0 (0.0%)	0 (0.0%)	0 (0.0%)
Secondary endpoints			
Obstructive CAD	NA	8 (25.8%)[d]	6 (19.4%)
Cardiovascular death at 1 yr	1 (1.3%)	1 (0.4%)	0 (0.0%)
ICA complications	0 (0.0%)	0 (0.0%)	0 (0.0%)

AMI, acute myocardial infarction; CAD, coronary artery disease; CNARTS, Central Northern Adelaide Renal and Transplantation Service; CVS, cardiovascular system; ICA, invasive coronary angiography.
[a]Renal transplant recipients who underwent vasodilatory or anatomical tests excluded (N = 19).
[b]No cardiac stress test before listing.
[c]Direct to ICA.
[d]Thirty-one patients underwent ICA following positive or invalid tachycardia-induced stress test.

days after renal transplantation in either the "low risk, no stress test required" or "tachycardia-induced stress test" cohorts (Table 2). Three patients (0.8%) experienced an AMI within 30 days after renal transplantation, all of which were non-ST-elevation myocardial infarctions. Two patients had previously undergone ICA within an 18-month period before transplantation with one undergoing CABG, resulting in complete, multivessel revascularization, and the other managed medically after being found to have an occluded saphenous vein graft. The third patient had ICA 5 years before transplantation, with mild diffuse irregularities noted and was not submitted to further provocative testing before listing for transplantation. Following his perioperative AMI, he underwent repeat ICA and had stenting to the culprit circumflex stenosis. This in retrospect was an inadvertent breach of the center's protocol. None were subjected to provocative testing before listing for transplantation.

Secondary Endpoints

Of the 27 patients with positive tachycardia-induced cardiac stress tests, 7 were found to have obstructive coronary artery disease on ICA (25.9%): 2 after a DSE (33.3%), 2 after an exercise myocardial perfusion scintigram (66.6%), 2 after a dobutamine myocardial perfusion scintigram (13.3%), and 1 after a dobutamine stress cMRI (50%) (Table 3). Of the 7 patients with a true-positive tachycardia-induced cardiac stress test, 2 underwent percutaneous coronary intervention (28.6%), 1 underwent CABG (14.3%), and 4 were treated medically (57.1%).

Of the 31 patients who proceeded directly to ICA, 6 were found to have obstructive coronary artery disease (19.3%). Of those, 2 underwent percutaneous coronary

Table 3. Tachycardia-induced stress test

	Total number	Negative investigation	Invalid investigation	Positive investigation	True positive stress test	PPV (%)[a]
Exercise stress ECG	11	10	0	1	0	0
Stress echocardiogram						
Exercise	42	40	2	0	NA	NA
Dobutamine	16	9	1	6	2	33.3
Myocardial perfusion scintigraphy						
Exercise	109	106	0	3	2	66.6
Dobutamine	78	62	1	15	2	13.3
Dobutamine stress cMRI	14	12	0	2	1	50.0
Total	270	239	4	27	7	25.9

cMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; NA, not applicable; PPV, positive predictive value.
[a]PPV for a positive tachycardia-induced stress test.

intervention (33%), 2 proceeded to CABG (33%), and 2 were treated medically (33%).

There were 2 deaths (0.5%) secondary to cardiovascular disease in patients with a functioning allograft within the first year of transplantation: 1 from the "tachycardia-induced stress test" cohort after a cerebrovascular accident and 1 from the low-risk "no stress test required" cohort after a cardiac arrest of unclear etiology.

During the 5-year study period, there were no procedure-related death, AMI, stroke, or significant access-site bleeding documented in the 62 ICAs that were performed before renal transplantation.

DISCUSSION

Cardiovascular disease is a leading cause of mortality and morbidity among patients with ESKD both before and after transplantation.[15,16] The pathophysiological mechanisms linking CKD with CAD remain to be fully elucidated but are clearly multifactorial in nature with inflammation,[17] oxidative stress,[18] uremia,[19] reduced nitric oxide bioavailability,[20] and vascular calcification[21] implicated. Observational data suggests a 5% rate of AMI at 6 months after kidney transplantation.[22,23] The accurate assessment of cardiovascular risk before noncardiac surgery can be problematic, and the medical complexity, comorbidity burden, and altered basic physiology of patients with CKD heightens concerns about the applicability of standard risk scoring systems to renal transplant candidates. Furthermore, there has been a marked shift in the age composition of transplant waitlists toward older recipients with increased cardiovascular risk. As a result, there is an increasing need for the reliable exclusion of clinically important obstructive coronary artery disease before the placement of patients with ESKD on an active renal transplant list.

Over the past 5 years, we have employed a cardiovascular assessment protocol before placing potential recipients on the active renal transplant list. Using this protocol, patients meeting low-risk criteria are listed without additional investigation for possible CAD. For all other asymptomatic patients, a noninvasive, tachycardia-induced screening stress test is performed to rule out physiologically significant CAD. Patients with a negative test result after achieving the target >85% maximal heart rate are listed. Those with an abnormal test result undergo ICA and revascularization if deemed necessary on prognostic grounds. Patients with symptoms consistent with angina and a concerning risk profile frequently proceed directly to ICA with the need for revascularization generally determined by the level of symptoms, degree of myocardium at risk, and the prognostic significance of the established CAD. Once on the active renal transplant list, repeat tachycardia-induced stress testing looking for "new" CAD is performed as clinically indicated in high-risk patients, annually for those patients that have had previous percutaneous coronary intervention, and at 36 months post–CABG and then annually thereafter.

Our retrospective review suggests that this approach truly identifies patients who are at a low risk of cardiovascular events early in the post–kidney transplant period. Our results show that asymptomatic, low-risk ESKD patients under 45 years and on dialysis for less than 2 years may safely proceed to renal transplantation based on clinical assessment without prior noninvasive coronary artery testing, with no deaths or periprocedural AMIs seen in this cohort up to 30 days after transplantation. More importantly, our data indicate that in all other asymptomatic ESKD patients, a valid, negative tachycardia-induced stress test predicts a favorable early cardiovascular outcome after renal transplantation with no cardiovascular mortality or AMI seen within 30 days in this cohort. In the 5-year study period, only 3 patients in the entire renal transplant cohort experienced an AMI within 30 days after transplantation, 2 of whom had previously undergone CABG and had ICA within 18 months of renal transplantation. They were listed without further

coronary testing according to our protocol, and a shift to yearly tachycardia-induced stress testing might have been warranted for this subgroup while they remain on the active transplant list. The third patient had ICA 5 years earlier and was placed on the active renal transplant without the provocative tachycardia-induced stress testing required as part of the center's protocol. There were no deaths secondary to cardiovascular disease within 30 days in our all-inclusive cohort, which was in keeping with the national rate of 0.003% in 2018 (N = 3).[24]

Although ICA remains the reference gold standard investigation for the assessment of clinically significant obstructive coronary artery disease, it is not a test for myocardial ischemia. Furthermore, it has multiple risks, including threat to residual renal function, which impacts patient survival in ESKD.[25–27] This provides impetus to the search for an alternative, reliable noninvasive coronary screening test before listing for renal transplantation. To date, there is a paucity of randomized controlled data comparing different forms of "provocative" testing in this cohort, and the data that are present were often derived from imaging modalities and yielded conflicting results. In a randomized study, De Vriese et al. compared dipyridamole to dobutamine as a cardiac stressor in a hemodialysis population undergoing myocardial scintigraphy.[28] They found that while the ability of both forms of provocative tests to accurately identify "angiographically significant" disease was poor, vasodilatory stress testing more accurately identified patients at high risk of adverse cardiac events than did dobutamine stress testing. This, however, may partly reflect the fact that 44.3% of the patients undergoing dobutamine stress myocardial scintigraphy failed to reach the 85% target heart rate for age and gender required for a valid test by our cardiovascular assessment criteria. In contrast, in the largest meta-analysis undertaken in this area by Wang et al., it was determined that DSE may be more accurate than myocardial perfusion scintigraphy in this patient cohort.[29] The authors postulated that one possible mechanism was the result of cardiac parasympathetic denervation, seen particularly in diabetic patients with chronic renal failure, which could decrease the relative efficacy of dipyridamole (routinely used in myocardial scintigraphy) compared with dobutamine (routinely used in stress echocardiography). Although we did not set out to compare vasodilatory and tachycardia-induced stress testing, we agree with Wang et al., supported by results of our invasive human coronary studies undertaken in stage 5 CKD patients receiving renal replacement therapy, demonstrating a reduced microvascular hyperaemic

response to intracoronary adenosine compared with well-matched non-ESKD controls subjects.[30]

This audit of 380 patients using our tachycardia-induced stress protocol has a number of strengths. First, our cohort is representative of the broader Australian transplant population, particularly in regard to baseline characteristics of transplant recipients.[31] Second, the outcome data are robust as no patients were lost to follow-up through use of the ANZDATA registry. Third, our center retains renal transplant recipients under its care for the first 3 months after transplantation, ensuring that follow-up and reported cardiac outcomes are complete. However, there are limitations, largely related to the observational and retrospective nature of this analysis. In addition, our cardiovascular data only extend to 1 year, and were this to be increased, we would expect to observe an increased incidence of adverse cardiac events. Also, the varying methodology used to assess ischemia and the several breaches of the general protocol that occurred are added weakness of the study. Finally, without an adequately powered randomized controlled trial, it remains uncertain whether our tachycardia-induced stress testing protocol is superior to other protocols that may include vasodilatory stress testing.

In conclusion, this retrospective study validated the effectiveness of a negative tachycardia-induced cardiac stress testing, when a target heart rate of 85% predicted for age and gender is achieved, in predicting the absence perioperative myocardial infarction and cardiovascular death following kidney-only transplant surgery within 30 days. No AMIs or cardiovascular deaths within 30 days after renal transplantation in patients with a negative tachycardia-induced stress test supports the listing of these patients for renal transplantation without the need for invasive coronary testing. Furthermore, we have demonstrated that no preliminary noninvasive testing for possible CAD is required before renal transplant listing for asymptomatic "low-risk" patients aged under 45 provided they are nonsmokers, do not have diabetes, and have been dialysis-dependent for less than 24 months.

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